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Dated: August 28, 2008 /Sharon M. Sintich Reg. No. 48,484/
Electronic Signature for Sharon M. Sintich:
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Docket No.: 9189
(01017/40451B)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Brockhaus et al.

Application No.: 08/444,790

Art Unit: 1646

Filed: May 19, 1995

Examiner: Z. Howard

For: HUMAN TNF RECEPTOR

**PETITION UNDER 37 C.F.R. §1.181 OR §41.3 AND
REQUEST FOR DESIGNATION OF NEW GROUNDS OF REJECTION**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants hereby petition the Director under 37 C.F.R. §1.181 (and, to the extent necessary, under 37 C.F.R. §§ 1.182 and 1.183) to review this petition on an expedited basis and correct the Examiner's failure to identify new grounds of rejection in the Examiner's Answer mailed August 14, 2008. This petition is timely filed within two months of the date of mailing of the Examiner's Answer. See MPEP §1207.03. Alternatively, if jurisdiction has passed to the Board of Appeals, please consider this a petition under 37 C.F.R. § 41.3 to the Chief Administrative Patent Judge, which is timely filed within fourteen days of the mailing date of the Examiner's Answer.

I. Statement of the Facts Involved

A. The Presently Pending Claims

The claims in the present application relate generally to fusion proteins comprising (a) a TNF-binding soluble fragment of a human TNF receptor (TNFR) having a molecular weight of about 75 kD, and (b) all of the domains of the constant region of a

human immunoglobulin heavy chain other than the first domain of said constant region. The TNFR of about 75 kD is also referred to as the “p75 TNFR.”

B. Relevant Prosecution History

As discussed below, Appellants’ evidence of unexpected results submitted in response to a non-final office action was not substantively considered in either the subsequent final office action or the advisory action. The substance of this evidence was considered for the first time in the Examiner’s Answer, which also put forth novel factual assertions and a new theory of rejection. For the reasons discussed in section III below, this new theory constitutes an improper new ground of rejection that was not identified as such.

In addition, the Examiner’s Answer asserted for the first time a novel interpretation of the claims as encompassing monomeric fusion proteins lacking a hinge domain. This new assertion was used to support a new basis for rejection. Finally, the Examiner’s Answer relied for the first time on a new rationale for its obviousness rejection, citing a different portion of a prior art reference that had never been previously cited or discussed.

On April 3, 2006, a non-final Office Action was issued which rejected the claims as lacking written description because the specification allegedly did not describe the complete p75 TNFR sequence. The Office Action also rejected the claims as obvious over two references, Dembic and Capon. The Dembic reference, cited for the first time in this Office Action, discloses p75 TNFR sequence. The Capon reference was cited for its general disclosure of fusion proteins comprising immunoglobulin fragments.

Appellants mailed a response on October 3, 2006. As part of their arguments regarding nonobviousness, Appellants submitted evidence of unexpected results for two different species of fusion proteins within the scope of the claims (extracellular domain of p75 fused to the hinge of IgG1 and extracellular domain of p75 TNFR fused to the hinge of IgG3). Appellants also stated their position that their claims were directed to fusion proteins that included hinge, CH2 and CH3 domains, and that these fusion proteins naturally formed

homodimers. The relevant portion of Appellants' response is reproduced below (emphasis added):

During the interview [of June 22, 2006], Applicants discussed the trimeric nature of tumor necrosis factor (TNF) alpha *and the homodimeric nature of the claimed fusion proteins*, which comprise soluble fragments of p75 tumor necrosis factor receptor (TNFR) fused to all of the domains of the constant region of a human immunoglobulin IgG heavy chain other than the first domain (CH1) of said constant region. The *immunoglobulin portion of the claimed fusion protein, which includes the hinge, second domain (CH2), and third domain (CH3) of the heavy chain constant region, naturally homodimerizes through cysteine bonding between the two hinge regions.* (Response dated October 3, 2006, page 10; emphasis added.)

On February 23, 2007, a final office action ("Final Action") was issued which maintained the written description rejections, albeit with a newly stated position and rationale. The obviousness rejection was also maintained over the same references, Dembic and Capon. Appellants' evidence of unexpected results was not considered, on the grounds that it was unnecessary to substantively consider unexpected results for embodiments of claims that were asserted to lack precise written description. The only portion of the Office Action which addressed Appellants' evidence is reproduced below in its entirety:

Applicants further argue that the 103 rejection should be withdrawn in view of a number of unexpected results associated with the claimed TNF-binding fusion proteins. Applicants present data supporting three categories of unexpected results: lack of aggregation ability; markedly reduced immunoglobulin effector function; and "binding affinity, kinetic stability and potency".

Applicants' arguments have been fully considered but are not found persuasive. The evidence of unexpected results presented by Applicants is not sufficient to overcome the rejection. Applicants' putative unexpected results appear to be generated using a fusion protein comprising the full-length extracellular domain of the insoluble 75 kD TNF binding receptor and portions of an immunoglobulin molecule. However, as set forth above, in the section "Claim Rejections – 35 U.S.C. 112, 1st paragraph, written description", the

specification does not provide a description of this particular species of fusion protein. There is no conception in the specification at the time of filing of this particular species of fusion protein. Therefore, the evidence of unexpected results found with this particular species of receptor-Ig fusion is not sufficient to overcome the obviousness of combining the teachings of Dembic in view of Capon. (Pages 18-19 of Final Action).

The Final Action acknowledged Appellants' claim construction, *i.e.*, that the claimed fusion proteins included a hinge which naturally homodimerizes via cysteine bonds: "Applicants argue that fusion of TNFR soluble fragments to immunoglobulin fragments for affinity purification does not provide motivation for construction of homodimeric fusion proteins (such as would be formed by the claimed proteins)." (Final Action, page 16). The Final Action did not propose any alternative claim construction which would encompass fusion proteins missing the hinge. Moreover, the explanation of why the rejection was maintained focused only on prior art teachings with respect to dimeric forms: "Therefore, the state of the prior art provides a motivation to use a dimeric form of the receptor for binding TNF ligand as taught by Capon . . ." (Page 17).

On August 2, 2007, Appellants submitted a response with declaratory evidence addressing the new position on written description set forth in the Final Action. Appellants reiterated their disagreement with the obviousness rejection.

On October 9, 2007, an advisory office action ("Advisory Action") was issued. The Advisory Action contained no additional discussion with respect to the obviousness rejection. Appellants' declaratory evidence regarding written description was admitted into the record. Appellants appealed and filed their appeal brief on February 25, 2008.

In the Examiner's Answer mailed on August 14, 2008, Appellants' evidence regarding unexpected results was substantively considered for the first time. The Examiner's Answer admits that most of Appellants' evidence constitutes unexpected results. For example, the Examiner did not dispute that the drastically reduced effector function (pages

64-65), the failure to form aggregating complexes (page 65), the increase in TNF neutralizing potency (page 66), the increased kinetic stability (page 67) and the improved inhibition of TNF (page 67) were each unexpected results.

Furthermore, the Examiner's Answer acknowledged that unexpected results sufficient to rebut obviousness could consist of unexpected results for a single member of a claimed subgenus or for a narrow portion of a claimed range. (Page 63) However, the Examiner's Answer newly alleged that "the skilled artisan could not ascertain a trend in the exemplified data that would allow him to reasonably extend the probative value thereof." (Page 64) The Examiner's Answer also newly stated that "Appellants do not provide any evidence that the unexpected results extend to the full range of the claimed genus of 'soluble fragments' of part (a) of each claim, including mutated variants of a 75 kD insoluble TNF receptor." (Page 64).

Moreover, the Examiner's Answer newly asserted that the claim language "all of the domains of the constant region of an IgG heavy chain other than CH1" included immunoglobulin fragments lacking a hinge domain, and stated for the first time that the claims were interpreted to encompass monomeric fusion proteins missing the hinge. As a result, the Examiner's Answer relied for the first time on the theory that a prior art teaching of monomeric fusion proteins missing a hinge domain rendered obvious Appellants' claims. (See page 61).

Furthermore, the Examiner's Answer cited to portions of Capon (cols. 7, 10 and 17) that had not been cited previously, and asserted a different teaching and motivation than explained previously. (See pages 61-62). In the Office Action mailed April 3, 2006, the Examiner referred to the following portions of Capon: col. 22, lines 5-6; col. 26, lines 24-26; col. 29, line 37; col. 30, lines 26-27; col. 31, lines 4-8 and Example 4 (starting at col. 40). (See page 11 of Action) In the Final Action, the Examiner cited the identical portions of Capon. However, in the Examiner's Answer, the following new portions of Capon were cited: col. 10, lines 10-12, col. 10, lines 27-28, col. 10, line 61, col. 17, lines 54-56, and col. 7, lines 13-16. (See pages 14-15 of Final Action). Thus, citations to cols. 7, 10 and 17 of

Capon are conspicuously absent from the portions of Capon cited in the previous office actions.

For the reasons discussed below, each of these new assertions constitutes a new theory of obviousness that is an improper new ground of rejection.

II. Relief Requested

Because of the imminent deadline for filing a reply brief, Applicants respectfully request that the Director (or the Chief Administrative Patent Judge) consider this petition on an expedited basis and issue a decision before the two month period for filing a reply brief expires.

Applicants respectfully request that the Director (or the Chief Administrative Patent Judge) render a decision directing the Examiner to:

(1) provide a corrected Examiner's Answer withdrawing the new grounds of rejection in the Examiner's Answer; or

(2) provide a corrected Examiner's Answer that properly identifies the new grounds of rejection and includes the approval of the TC Director or designee.

III. Statement of Reasons That Requested Relief Should Be Granted

Any new ground of rejection made by an examiner in an answer must be prominently identified as a new ground of rejection. MPEP §§ 1207.02 and 1207.03. The test for "whether a rejection is considered 'new' in a decision by the board [or in an examiner's answer] is whether appellants have had fair opportunity to react to the thrust of the rejection". *In re Kumar*, 418 F. 3d 1361, 1368, 76 U.S.P.Q.2d 1048 (Fed. Cir. 2005), citing *In re Kronig*, 539 F. 2d 1300, 1302 (CCPA 1976). "Where the board makes a decision [or an examiner makes a rejection] advancing a position or rationale new to the proceedings, an applicant must be afforded an opportunity to respond to that position or rationale by

submission of contradicting evidence.” *In re DeBlauwe*, 736 F. 2d 699, 706 n.9, 222 U.S.P.Q. 191 (Fed. Cir. 1984).

A. New Ground of Rejection Relating to Untimely Analysis of Unexpected Results

As explained above in section I.B., Appellants had previously provided evidence of unexpected results, with respect to two different species within the scope of Appellants’ claims, when Appellants responded to the non-final office action. This evidence was never substantively considered in the final action or the advisory action, and was only addressed for the first time in the Examiner’s Answer. Therefore, the analysis of the unexpected results provided for the first time in the Examiner’s Answer is untimely.

While the Examiner’s Answer admits the unexpected nature of the results, the Answer takes the position for the first time that the results are not sufficiently representative of the full range of TNF-binding soluble fragments of p75 TNFR. The Examiner’s Answer also asserts for the first time that the data do not show a trend that permits the skilled artisan to reasonably extend the probative value of the evidence to the full range of the claimed genus. For example, see the paragraph spanning page 63-64 of the Examiner’s Answer. (Attached as Appendix A).

These aspects of the Examiner’s Answer are a new assertion and novel theory that constitute a new ground of rejection. Consideration of this new theory on appeal would be inappropriate because Appellants have not had a fair opportunity to respond, and consequently the record does not adequately address this issue. Moreover, advancing a novel position or rationale on appeal, when new evidence and amendments cannot be introduced, deprives Appellants of administrative due process.

The present situation is analogous to that in *In re DeBlauwe, supra*, where despite appellants' arguments throughout prosecution that articles with the claimed expansion ratios unexpectedly overcame a longstanding problem, the Board and the Examiner failed to state their position that there was no objective evidence of unexpected results. Because of

this lack of notice and opportunity to respond, the Federal Circuit vacated the Board's decision and remanded the case, stating:

In view of the PTO's failure to challenge the sufficiency of appellants' rebuttal evidence until this appeal, when appellants could no longer offer evidence, we conclude that it is necessary to vacate the board's decision on claims 42-51 and 53 and to remand the case to afford appellants the opportunity to submit objective evidence of unexpected results. *In re DeBlauwe*, 736 F. 2d at 706.

Thus, in this case, as in *In re DeBlauwe*, the PTO's failure to challenge the extent of Appellants rebuttal evidence until this appeal, when there is no longer an opportunity to offer additional evidence, requires that the allegations with respect to unexpected results be deemed a new ground of rejection. Failure to identify this as a new ground of rejection deprives Appellants of administrative due process.

B. New Ground of Rejection Relating to Newly Asserted Claim Construction

Appellants clearly stated during prosecution their position that the pending claims were directed to fusion proteins that included hinge, CH2 and CH3 domains, and that these fusion proteins naturally formed homodimers. Appellants' position was explained during the in-person interview of June 22, 2006 and in their response mailed October 3, 2006, as discussed above in section I.B. Moreover, Appellants' position was acknowledged in the Final Action mailed February 23, 2007, and no contrary claim construction was advanced by the Examiner at that time.

The advancement of a novel claim interpretation in the Examiner's Answer, *i.e.*, that the claims encompass monomeric fusion proteins missing the hinge, is a new ground of rejection. For example, see the paragraph spanning pages 58-59 the majority of page 61 of the Examiner's Answer and the first paragraph on page 62 of the Examiner's Answer. (Attached as Appendix A).

The present situation is analogous to *In re Kumar, supra*, in which the Board instituted a new theory of rejection by relying for the first time on overlapping values calculated from a reference's disclosure. The Federal Circuit considered that the "identification of the values deemed to overlap is material to the rejection. . . . In calculating

the overlapping values, the Board found facts not found by the examiner regarding the differences between the prior art and the claimed invention, which in fairness required an opportunity for response.” *In re Kumar*, 418 F. 3d at 1367-1968, n. 7. The Federal Circuit concluded that “the Board’s calculations and its decision based thereon constituted a new ground of rejection, and should have been so treated.” *In re Kumar* 418 F. 3d at 1368.

Similarly, in this case, the novel claim construction is highly material to the obviousness rejection because it permits reliance on alternative teachings in the prior art that are not applicable under Appellants’ acknowledged claim construction. Moreover, the Examiner’s novel claim interpretation depends on new factual assertions with respect to claim terms that Appellants have not had an opportunity to rebut. Introduction of these new issues when Appellants can no longer introduce evidence, *e.g.*, with respect to the meaning of the claim terms, thus constitutes a new ground of rejection and should be identified as such. Failure to identify this as a new ground of rejection deprives Appellants of administrative due process.

C. New Ground of Rejection Relating to Reliance on Different Portion of Capon

Finally, the novel reliance in the Examiner’s Answer on a different portion of Capon that had not previously been cited, in order to support a newly asserted rationale for obviousness, constitutes a new ground of rejection. Capon describes hundreds of different variations of immunoglobulin fusion proteins that include many different permutations of immunoglobulin domains, and a variety of multimeric (tetrameric, trimeric, homodimeric, heterodimeric) and monomeric forms. As explained above in section I.B., citations to newly relied-upon portions of Capon, cols. 7, 10, and 17, are wholly absent from the April 3, 2006 and February 23, 2007 actions.

The Examiner is obligated to designate the particular teaching of a reference relied on, particularly when the reference is complex or describes inventions other than that claimed. 37 C.F.R. 1.104(c)(2) states:

When a reference is complex or shows or describes inventions other than that claimed by the applicant, the particular part relied on must be designated as nearly as practicable. The

pertinence of each reference, if not apparent, must be clearly explained and each rejected claim specified.

In the present case, Capon's disclosure is not only complex but also describes a variety of different types of immunoglobulin fusion proteins that are not pertinent to the presently pending claims.

There are numerous examples where the Federal Circuit or its predecessor court have held that new aspects of a rejection are a novel ground of rejection which require remand to provide Appellants with a full and fair opportunity to respond. *See, e.g., In re Weichert*, 370 F. 2d 927, 152 U.S.P.Q. 247 (CCPA 1967) (new ground of rejection exists when Board relies on a different portion of a cited reference); *In re Waymouth*, 486 F. 2d 1058, 179 U.S.P.Q. 627 (CCPA 1973), amended on other grounds after rehearing, 489 F. 2d 1297, 180 U.S.P.Q. 453 (CCPA 1974) (Board's affirmance of same statutory rejection for different reasons is a new ground of rejection).

The present situation is closely parallel to *In re Weichert*, in which the Court of Customs and Patent Appeals (CCPA) concluded that "when a rejection is factually based on an entirely different portion of an existing reference the appellant should be afforded an opportunity to make a showing of unobviousness vis-a-vis such portion of the reference." *In re Weichert*, 370 F. 2d at 964. In this case, Appellants have not been afforded an opportunity to provide evidence, *e.g.* regarding what the newly cited portions of Capon teach one of ordinary skill, or regarding enablement, motivation or suitability of the claimed fusion proteins according to the Examiner's newly asserted rationale. Failure to identify the reliance on a different portion of Capon as a new ground of rejection thus deprives Appellants of administrative due process.

CONCLUSION

In accordance with the Administrative Procedure Act, the PTO must assure that an applicant's petition is fully and fairly treated at the administrative level, without interim need for judicial intervention. See *Dickinson v. Zurko*, 527 U.S. 150, 154, 144 L. Ed. 2d 143, 119 S. Ct. 1816 (1999) (the PTO is an agency subject to the Administrative Procedure Act). Appellants would be denied administrative due process if the Examiner were permitted to institute these new theories of rejection without designating them as new grounds for rejection.

Applicants believe that the requested relief should be granted, for all of the reasons explained above, and respectfully solicit a prompt decision on all issues before the time period for filing a reply brief expires. This petition is submitted with the requisite fee under 37 C.F.R. 1.17(f). The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 13-2855, under Order No. 01017/40451B.

Dated: August 28, 2008

Respectfully submitted,

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